IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Lyons, et al Customer No.: 51957 Serial No.: 10/826,843 Filed: April 15, 2004 For: **DRUG DELIVERY TO THE BACK OF THE EYE**	Group Art Unit: 1614 Confirmation No. 2070 Examiner: Zohreh A. Fay FILED ELECTRONICALLY

Commissioner of Patents and Trademarks
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Dear Sir:

This appeal is taken from the rejection of all of the claims in an Examiner's action mailed May 9, 2007. Oral hearing is waived.

(1) REAL PARTY IN INTEREST

This patent application is assigned to Allergan, Inc, having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612, via an assignment document recorded at Reel/Frame 015943/0127 on October 27, 2004.

(2) RELATED APPEALS AND INTERFERENCES

There is a pending appeal for Patent Application Serial No. 10/121,076, filed April 12, 2002 which contains related issues to the present case.

(3) STATUS OF CLAIMS

Claims	Status
1-19	Rejected, Appealed
20	Cancelled
21-23	Rejected, Appealed
24-25	Cancelled
26	Rejected, Appealed
27	Cancelled

(4) STATUS OF AMENDMENTS

Claims 20, 24, 25, and 27 were cancelled to reduce the number of issues to be considered on appeal.

(5) SUMMARY OF THE CLAIMED SUBJECT MATTER

1. Claim 1 is drawn to a method of delivering a therapeutically effective amount of a therapeutically active agents to structures in the back of the eye. (Specification, p. 6, lines 5-10). This is accomplished by topically administering a composition comprising a therapeutically active agent and a cyclodextrin derivative to the eye of a mammal in need thereof. (Specification, p. 6, lines 5-18 and p. 11, lines 28-32).

2. Claim 19 is drawn to a pharmaceutical product containing a composition comprising a therapeutically active agent and a cyclodextrin derivative, wherein the composition has an ophthalmically acceptable pH. (Specification, p. 4, lines 13-16 and p. 11, lines 28-32). The composition is in a container suitable for dispensing drops of the composition to a mammal in need thereof, and the product has a label which indicates that the product is useful for treatment of a disease or condition affecting the back of the eye. (Specification, p. 4, 17-20).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Obviousness

Examiner erroneously rejected claims 1-19, 21-23, and 26 under 35 U.S.C. § 103 as being anticipated by Helberg et. al. (U.S. Patent No. 6,646,001), Lyons (U.S. Patent No. 6,933,289), and Canadian Patent Application 2498233.

ARGUMENT

People with sight-threatening diseases affecting the retina and other structures in the back of the eye need to have a drug delivered to those structures for effective treatment. At the time of filing, this was generally done by injecting the drug into the person's eye. Applicants have invented a method of treating the person by administering a topical eye drop instead of sticking a needle in the person's eye. Unfortunately, Examiner erroneously believes that this invention is not patentable.

THE CLAIMS ARE ENABLED BECAUSE THE SPECIFICATION PROVIDES SUFFICIENT GUIDANCE FOR PRACTICING THE INVENTION.

Examiner rejected the claims for lack of enablement. Enablement merely requires that the specification provide "sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. " MPEP 2164.01. If Applicants understand the rejection correctly, it appears that Examiner believes the claims are too broad to be enabled because the specification allegedly does not provide enough examples of therapeutically active compounds that would work, and thus undue experimentation would be required.

The specification cites about 400 different examples of therapeutically active agents. (See p. 6, line 22 to p. 15, line 15.) Thus, a broad scope of the "how to make" requirement is satisfied.

Applicants have shown that cyclodextrin and cyclodextrin derivatives deliver prednisolone to the back of the eye. While the mechanism of this delivery is not known, it is reasonable to believe that it is related to the ability of cyclodextrin and cyclodextrin derivatives to complex lipophilic compounds and/or form inclusion compounds. As pointed out by Examiner, combinations of drugs and cyclodextrins or cyclodextrin

derivatives have been studied extensively. Thus, the known literature provides ample guidance to a person of ordinary skill to determine which compounds are likely to work in the claimed methods.

Examiner appears to believe that the "how-to-use" requirement makes it necessary for Applicants to do extensive testing of the claimed compounds in order for the enablement requirement to be satisfied. This is contrary to established law.

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of…analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public. In re Bundy, 642 F.2d 430, 434 209 USPQ 48, 52 (C.C.P.A. 1981).

Applicants have discovered a method that avoids the significant unpleasantness of using a needle or surgery to administer a drug to the back of the eye. Thus, to further public interest, filing does not require "specific testing of thousands of" compounds as Examiner appears to believe is necessary.

Finally, although Applicants have shown that the invention works, enablement does not require that Applicant provide evidence that the invention works: "lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." MPEP 2164.02. "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.04

Thus, if Examiner doubts that the claimed method works, she has the burden of supplying acceptable evidence or reasoning to support this doubt before an enablement rejection can be made. Since such evidence has not been provided, the claims should be presumed to be enabled. Therefore, the enablement rejection was improper.

THE CLAIMS ARE NOVEL BECAUSE NO PRIOR ART TEACHES USING CYCLODEXTRIN DERIVATIVES TO DELIVER DRUGS TO THE BACK OF THE EYE.

Claims 1-15, 19, 21-23, and 26 were rejected as being anticipated by Guy (U.S. Patent No. 5,576,311). Claims 1-19, 21-23, and 26 were rejected as allegedly being anticipated by WO02089815. Anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The present claim requires that a composition comprising the therapeutically active agent and the cyclodextrin derivative be administered “to an eye of a mammal in need thereof.” The “need thereof” referred to is the need to have a therapeutically effective amount of the therapeutically active agent delivered to one of the structures of the back of the eye, i.e. the person would have a condition or disease that would require delivery of the therapeutically active agent to one of those back of the eye structures.

The Federal Circuit has held that to anticipate a method of treating an animal or human by administering a composition to the animal or human, the prior art must teach administering the composition for the purpose specified in the claims: “[i]n other words, administering the claimed vitamins in the claimed doses for some purpose other than treating or preventing macrocytic-megaloblastic anemia is not practicing the claimed method, because Jansen limited his claims to treatment or prevention of that particular condition in those who need such treatment or prevention.” *Jansen v. Rexall Sundown,*

Inc., 342 F.3d 1329, 1334 (Fed. Cir. 2003). Neither of the references teaches administration of the composition for the purpose of delivering the drugs to the particular structures of the eye cited in the claims. Therefore, the claims are not anticipated.

Based upon what Examiner has stated in the May 9 Office Action, it appears that she believes that if a composition is known, no newly discovered use of that composition is patentable because the composition is inherently useful for that newly discovered use. (p. 3). However, *Jansen* makes it clear that this is not the case, and that different uses of a known composition are patentable over one another.

THE CLAIMED METHOD IS NOT OBVIOUS BECAUSE IT IS NOT SUGGESTED IN THE PRIOR ART AND BECAUSE APPLICANTS PROCEDED CONTRARY TO ACCEPTED WISDOM IN THE ART.

The prior art does not suggest using cyclodextrin derivatives to deliver drugs to the back of the eye.

Using cyclodextrin derivatives to deliver drugs to the back of the eye is not taught or suggested in the prior art. MPEP 2143 states that "the prior art reference (or references when combined) must teach or suggest all the claim limitations." Examiner has merely alleged that the method is inherent because the composition is known. She has not explained, for example, how a prior art treatment of a disease would suggest treating a disease requiring back of the eye delivery of a drug using the compositions of the claims. Neither has she explained how one of the prior art methods would necessarily: 1) be practiced on a mammal having a condition or disease requiring delivery of a drug to the back of the eye, and 2) use a composition described in the claims in such a way that a therapeutically effective amount of the required drug would be delivered to the back of the eye structure. An obviousness rejection requires an explicit analysis, not merely conclusory statements about inherency. See *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (U.S. 2007) quoting *In re Kahn,* 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot be

sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). Therefore, Examiner has failed to meet her burden of showing the claims are obvious.

Accepted wisdom in the art teaches that injections into the eye are necessary, and that eye drops do not work to deliver drugs to the back of the eye.

These claims are drawn to a method that accepted wisdom taught was not possible. "[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145 (X)(D)(3) citing *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Consider the following statement from a publication of a patent application that was filed in 2005 (US 2007/0020336, NOT PRIOR ART) by Loftsson, who has several patents and publications regarding using cyclodextrins and cyclodextrin derivatives in pharmaceutical compositions.

> It is generally accepted that eye drops are ineffective and of little benefit in delivering drugs in therapeutic concentrations to the posterior segment of the eye (Myles et al 2005; Raghava et al 2004; Yasukawa et al 2005). Therefore various approaches have been developed where drugs are injected into the vitreous cavity (Jonas 2005), injected under the conjunctiva or tenon's capsule and various devices invented that may be introduced into the eye (Yasukawa et al 2005). All of these approaches are based on the premise that non-invasive topical methods to effectively deliver drugs, such as corticosteroids, to the posterior segment of the eye are not available, and invasive methods are the only alternative (Myles et al 2005; Raghava et al 2004; Yasukawa et al 2005; Beeley et al 2005).

Thus, Applicants have invented a method of delivering drugs to the back of the eye which avoids the unpleasant experience of putting a needle in the eye. This was done contrary to the accepted wisdom in the art "that eye drops are ineffective and of

little benefit in delivering drugs in therapeutic concentrations to the posterior segment of the eye." Therefore, the claims are not obvious.

Applicants therefore request that the Board direct the Examiner to pass the claims to issue.

Dated: November 30, 2007

Respectfully submitted,

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(8) CLAIMS APPENDIX

1. (Rejected) A method comprising

topically administering a composition to an eye of a mammal in need thereof, said method being effective in delivering a therapeutically effective amount of a therapeutically active agent to a structure or combination of structures of the eye selected from the vitreous humor and structures posterior to the vitreous humor; said composition comprising:

a. an effective amount of the therapeutically active agent, or a pharmaceutically acceptable salt or prodrug thereof, to provide a therapeutically effective amount of the therapeutically active agent to said structure or combination of structures of the eye, and
b. an effective amount of a cyclodextrin derivative to provide said therapeutically effective amount of said therapeutically active agent to said structure or combination of structures of the eye

wherein the cyclodextrin derivative is selected from the group consisting of hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether-γ-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin, dimaltosyl-β-cyclodextrin, and combinations thereof.

2. (Rejected) The method of claim 1 wherein said mammal is a human.

3. (Rejected) The method of claim 1 wherein said therapeutically active agent, or salt or prodrug thereof, is water-insoluble.

4. (Rejected) The method of claim 1 wherein said therapeutically active agent, or salt or prodrug thereof, is water-soluble.

5. (Rejected) The method of claim 1 wherein said therapeutically active agent is not administered to reduce intraocular pressure.

6. (Rejected) The method of claim 1 wherein said therapeutically active agent is not administered to treat allergic conjunctivitis.

7. (Rejected) The method of claim 1 wherein said therapeutically active agent is not administered to treat dry eye.

8. (Rejected) The method of claim 1 wherein said therapeutically active agent is not administered to treat a condition affecting the front of the eye.

9. (Rejected) The method of claim 1 comprising a β-cyclodextrin derivative.

10. (Rejected) The method of claim 1 comprising a β-cyclodextrin derivative and a water-soluble polymer.

11. (Rejected) The method of claim 1 comprising prednisolone acetate, hydroxypropyl-β-cyclodextrin, and hydroxypropylmethylcellulose.

12. (Rejected) The method of claim 1 comprising a γ-cyclodextrin derivative.

13. (Rejected) The method of claim 5 comprising prednisolone acetate.

14. (Rejected) The method of claim 5 wherein said cyclodextrin derivate is hydroxypropyl-γ-cyclodextrin.

15. (Rejected) The method of claim 5 which further comprises a cellulose derivative.

16. (Rejected) The method of claim 5 which further comprises hydroxypropylmethylcellulose having a concentration less than 1%.

17. (Original) The method of claim 5 comprising from 0.05% to 0.4% hydroxypropylmethylcellulose.

18. (Rejected) The method of claim 5 comprising about from 0.1% to 0.25% hydroxypropylmethylcellulose.

19. (Rejected) A pharmaceutical product comprising
a solution comprising a therapeutically active agent, or a pharmaceutically active salt or a prodrug thereof, and a cyclodextrin derivative, wherein said solution has an ophthalmically acceptable pH, and wherein the cyclodextrin derivative is selected from the group consisting of hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether-γ-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxyethyl-γ-cyclodextrin, dihydroxypropyl-β-cyclodextrin, glucosyl-β-cyclodextrin, diglucosyl-β-cyclodextrin, maltosyl-β-cyclodextrin, maltosyl-γ-cyclodextrin, maltotriosyl-β-cyclodextrin, maltotriosyl-γ-cyclodextrin, dimaltosyl-β-cyclodextrin, and combinations thereof;

a container suitable for dispensing drops of said solution to the eye of a mammal in need of treatment by said therapeutically active agent, a pharmaceutically active salt or prodrug thereof, and

a package which indicates that said product is useful for treatment of a disease or condition affecting the back of the eye.

20. (Cancelled)

21. (Rejected) The product of claim 19 wherein said therapeutically active agent is not intended to reduce intraocular pressure.

22. (Rejected) The product of claim 19 wherein said therapeutically active agent is not intended to treat a condition affecting the front of the eye.

23. (Rejected) The composition of claim 20 comprising from 0.1% to 2% prednisolone acetate and from 1% to 30% of the cyclodextrin derivative.

24. (Cancelled)

25. (Cancelled)

26. (Rejected) The method of claim 1, wherein the therapeutically active agent is a corticosteroid.

27. (Cancelled)

(9) EVIDENCE APPENDIX

The following cited evidence is appended hereto in the pages that follow.

1. US 2007/0020336

(10) RELATED PROCEEDINGS APPENDIX

No decision has been rendered by the Board or a court regarding the appeal for Patent Application Serial No. 10/121,076, filed April 12, 2002. Therefore, nothing is included in this Appendix.